

Numerical simulation of the evolution of wound healing in the 3D environment

Abstract

Numerical simulation of the wound healing behaviour by considering the coupled reaction-diffusion, transport and viscoelastic system is vital in investigating the mechanical stress field induced by cell migration. In this work, numerical simulation is viewed in three-dimensional space during a time course of the wound healing. Previous authors have either considered a mathematical simulation of wound healing from one-dimensional case or have not considered the coupled system as is the case here. Therefore, to our knowledge, this is the first article to consider the numerical simulation of the coupled reaction-diffusion, transport and viscoelastic system during wound healing. Firstly, two-dimensional evolution of wound healing is developed to compare our results with published data. Then the work is extended to three-dimensional wound healing, which is the main focus.

Comment [Han jz1]: The abstract part is not concise enough.

Keywords: Numerical simulation; wound healing; reaction-diffusion; transport; viscoelastic system.

Comment [Han jz2]: The keyword is inaccurate.

1 Introduction

Wound healing is a complex phenomenon. Different authors model this healing process differently by considering specific parameters while ignoring other parameters from the mathematical point of view. Parameters mainly utilized involve extracellular matrix, wound contraction, cell traction, and angiogenesis [1,2,3,4,5,6]. McDougall, Dallon [7] developed a mathematical model of fibroblast cell migration and collagen deposition following a dermal wound. Due to the chemoattractant gradient, it was found that fibroblasts move rapidly into the damaged tissue to replace the dead cells. Furthermore, this study revealed how the complex wound structure is affected during wound healing.

Murray and Oster [8] developed a one-dimensional case of coupled reaction-diffusion, transport and viscoelastic systems and studied cell traction to create patterns and form in morphogenesis. This was the first study to derive this system from studying morphogenesis during wound healing. These equations were also put in the proper form by performing non-dimensionalization [8]. Murray and Oster also developed other models to study cell traction to establish patterns and structure in morphogenesis in the evolution of wound healing. Later, Sherratt, Martin [9] developed mathematical models to account for wound healing in embryonic and adult epidermis. They studied the mechanisms of epidermal repair in embryos and adults. Furthermore, they accounted for actin alignment during embryonic wound healing using the mechanical model. In contrast, reaction-diffusion was used to find the impact of growth factors during wound healing in adults. In 1994, Dale, Maini [2] proposed a reaction-diffusion model to study the mechanisms involved in healing corneal surface wounds. This study found that some of their solutions for cell density and epidermal growth factors evolved into travelling waves, while others failed to develop into travelling waves.

Comment [Han jz3]: There is no need to quote the same article many times in a sentence.

Cumming, McElwain [10] investigated the role of the cytokine transforming growth factor-beta during the healing and scar development using the mathematical model. This model reveals the history of using the reaction-diffusion equation to model processes involved during wound healing. It was also found in the same paper that fibroblasts quickly populate the wound within four days following the injury to the tissue in response to the chemotactic gradient. Several models on wound healing using the reaction-diffusion equation have been well documented [11]. These include epidermis and dermis damage models, chronic disorders and solid tumour growth. Jorgensen and Sanders [12] gave a comprehensive review of the advances in mathematical modelling of wound healing and wound closure. These models include only investigate the biomechanics of the tissue during the wound healing process [13,14,15,16]. Another great review of computational wound healing models was previously carried out [17].

Recently, agent-based modelling has been adopted to model the dynamics involved during wound healing. One such model was developed to investigate how fibroblasts integrate local chemical, structural, and mechanical cues as they deposit and remodel collagen[18]. This model represented a section of the heart myocardium perpendicular to the epicardial surface on the heart's left ventricle. Later, this model was coupled with the finite element model to get realistic deformations from the finite element model to drive the agent-based model [19].

Comment [Han jz4]: Others' achievements need to be summarized and refined, and then lead to their own innovations.

The current study focuses on skin wound healing, modelled by a coupled system of reaction-diffusion, transport and viscoelastic equations. This system is solved numerically using finite difference schemes. We began by solving the two-dimensional case compared with previously published data. Then this model is extended to a three-dimensional case.

2 The Governing Model

2.1 Two-dimensional case

The wound healing model consists of the following system of equations.

$$\begin{aligned} \frac{\partial n}{\partial t} + \frac{\partial}{\partial x} \left[n \frac{\partial u}{\partial t} + \chi(\rho) n \frac{\partial \rho}{\partial x} - D(\rho) \frac{\partial n}{\partial x} \right] &= P(n, \rho), \\ \frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x} \left(\rho \frac{\partial u}{\partial t} \right) &= B(n, \rho), \\ \frac{\partial}{\partial x} \left[n \frac{\partial^2 u}{\partial x \partial t} + E \frac{\partial u}{\partial x} + \tau(n, \rho) \right] &= F(n, \rho), \end{aligned} \quad (1)$$

where,

- $\rho(x, t)$ is the ECM density
- n is the cell density
- u is the displacement
- Body forces, F , measure the ECM matrix's strength to the underlying tissues. Generally, the ECM matrix is attached elastically to the epithelial layer
- Traction forces depend on the adhesion between the cell surface and collagen fibres.

$$\tau(n, \rho) = \frac{T_0 n \rho}{R^2 + \rho^2} \quad (2)$$

The following assumptions we used in this model:

- We set the cell and the ECM density to one for normal tissue.
- Fibroelastic cells proliferate according to a logistic growth law,

$$P = rn(1 - n),$$

where r is the linear growth rate and $r > 0$.

- Set $D > 0$ as a constant.
- The collagen biosynthesis and degradation rate are assumed to be proportional to n and $-np$.

$$B = \epsilon n(1 - p),$$

- and where ϵ is very small to introduce the fact that the ECM remodelling takes more time than the proliferation of cells.
- The positive parameters μ and E quantify the viscous and elastic contributions.
- We neglect haptotactic contributions.

The following boundary conditions we utilized around the wound domain:

$$\begin{aligned}\frac{\partial \mathbf{n}}{\partial \mathbf{x}}(\mathbf{0}, t) &= \frac{\partial \rho}{\partial \mathbf{x}}(\mathbf{0}, t) = \mathbf{u}(\mathbf{0}, t) = \mathbf{0}, \\ \mathbf{n}(\infty, t) &= \rho(\infty, t) = \mathbf{1}, \\ \mathbf{u}(\infty, t) &= \mathbf{0},\end{aligned}\quad (3)$$

with the initial conditions given by

$$\begin{aligned}\mathbf{n}(\mathbf{x}, 0) &= \mathbf{H}(\mathbf{x} - \mathbf{1}), \\ \rho(\mathbf{x}, 0) &= \rho_i + (1 - \rho_i)\mathbf{H}(\mathbf{x} - \mathbf{1}) \\ \mathbf{u}(\mathbf{x}, 0) &= \mathbf{0},\end{aligned}\quad (4)$$

where \mathbf{H} is the Heaviside functions.

2.2 Three-dimensional case

The same system was upgraded to a two-dimensional case as given below

$$\begin{aligned}\frac{\partial n}{\partial t} + \operatorname{div}\left[n\frac{\partial \mathbf{u}}{\partial t} + \chi(\rho)n\nabla\rho - D(\rho)\nabla n\right] &= P(n, \rho) \\ \frac{\partial \rho}{\partial t} + \operatorname{div}\left(\rho\frac{\partial \mathbf{u}}{\partial t}\right) &= B(n, \rho) \\ -\operatorname{div}\left[\mu\frac{\partial(\nabla \mathbf{u})}{\partial t} + E\nabla \mathbf{u} + \tau(n, \rho)\mathbf{I}\right] + F(n, \rho) &= 0\end{aligned}\quad (5)$$

We now divide the displacement in u_1 and u_2 for the movement in x and y direction, respectively:

$$\begin{aligned}\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}\left[n\frac{\partial u_1}{\partial t} + \chi(\rho)n\frac{\partial \rho}{\partial x} - D(\rho)\frac{\partial n}{\partial x}\right] + \frac{\partial}{\partial y}\left[n\frac{\partial u_2}{\partial t} + \chi(\rho)n\frac{\partial \rho}{\partial y} - D(\rho)\frac{\partial n}{\partial y}\right] &= P(n, \rho), \\ \frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}\left(\rho\frac{\partial u_1}{\partial t}\right) + \frac{\partial}{\partial y}\left(\rho\frac{\partial u_2}{\partial t}\right) &= B(n, \rho), \\ -\left[\mu\left(\frac{\partial(\frac{\partial u_1}{\partial t})}{\partial t} + \frac{\partial(\frac{\partial u_2}{\partial t})}{\partial t}\right) + E\left(\frac{\partial u_1}{\partial x} + \frac{\partial u_2}{\partial y}\right) + \left(\frac{\partial \tau}{\partial t}\right)\right] + F(n, \rho) &= 0,\end{aligned}\quad (6)$$

with the following boundary conditions:

$$\begin{aligned}n(x, 0, t) &= n(x, \infty, t) = \rho(x, 0, t) = \rho(x, \infty, t) = 1, \\ \frac{\partial n}{\partial x}(0, y, t) &= \frac{\partial n}{\partial x}(\infty, y, t) = \frac{\partial \rho}{\partial x}(0, y, t) = \frac{\partial \rho}{\partial x}(\infty, y, t) = 0, \\ u(x, 0, t) &= u(x, \infty, t) = u(0, y, t) = u(\infty, y, t) = 0.\end{aligned}\quad (7)$$

Comment [Han jz5]: Three-dimensional and two-dimensional assumptions are the same?

3 Finite difference scheme

We apply the implicit finite difference on the spatial variable and the Euler scheme for the time variable in the following sections. It has already been proved that an implicit scheme converges, and it is stable unconditionally [20,21].

3.1 Three-dimensional case

We use forward or backward Euler depending on the direction of the flow.

If $\frac{\partial u}{\partial t} < 0$ we have;

$$C = \frac{n_{i+1}^N(u_{i+1}^{N+1} - u_{i+1}^N) - n_i^N(u_i^{N+1} - u_i^N)}{dx},$$

$$A = \frac{\rho_{i+1}^N(u_{i+1}^{N+1} - u_{i+1}^N) - \rho_i^N(u_i^{N+1} - u_i^N)}{dx}.$$

If $\frac{\partial u}{\partial t} > 0$ we have

$$C = \frac{n_i^N(u_i^{N+1} - u_i^N) - n_{i-1}^N(u_{i-1}^{N+1} - u_{i-1}^N)}{dx},$$

$$A = \frac{\rho_i^N(u_i^{N+1} - u_i^N) - \rho_{i-1}^N(u_{i-1}^{N+1} - u_{i-1}^N)}{dx}.$$

Substituting all the above discrete forms into equation **Error! Reference source not found.** and discretizing the remaining terms, we get:

$$n_i^{N+1} = n_i^N - C - \frac{\chi_i n_i dt (\rho_{i+1}^N - \rho_i^N) - \chi_{i-1} n_{i-1} dt (\rho_i^N - \rho_{i-1}^N)}{dx^2} + \frac{D_i dt (n_{i+1}^N - n_i^N) - D_{i-1} dt (n_i^N - n_{i-1}^N)}{dx^2} + dt P(n, \rho)_i,$$

$$\rho_i^{N+1} = \rho_i^N - A + B(n, \rho)_i,$$

$$\left(\frac{\mu}{dt} + E\right) \left(\frac{-u_{i+1}^{N+1} + 2u_i^{N+1} - u_{i-1}^{N+1}}{dx^2}\right) + F_i = \frac{\mu}{dt} \left(\frac{-u_{i+1}^N + 2u_i^N - u_{i-1}^N}{dx^2}\right) + \frac{\tau_{i+1}^N - \tau_i^N}{dx},$$

where $F_i = s\rho_i^N u_i^{N+1}$. (8)

The above discrete equations result in algebraic equations, which can be turned into a matrix form. Considering only the last equation in **Error! Reference source not found.**, we get the following matrix form of the equations:

$$\left(\frac{\mu}{dt} + E\right) \mathbf{B} \mathbf{u}^{N+1} = \frac{\mu}{dt} \mathbf{B}_1 \mathbf{u}^N + \boldsymbol{\tau}^N. \quad (9)$$

Below is an example of the form of the tridiagonal matrix from B :

$$\frac{1}{dx^2} \begin{pmatrix} 2 & -1 & 0 & \dots & 0 \\ -1 & 2 & -1 & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & -1 & 2 & -1 \\ 0 & \dots & 0 & -1 & 2 \end{pmatrix} \quad (10)$$

3. 2 Two-dimensional case

In the following, we derive the discrete form of the time derivate, which is dependent on the flow direction or direction of the migration of the cells within the wound.

Flow: x direction

If $\frac{\partial u_1}{\partial t} < 0$ we have:

$$C_1 = \frac{n_{i+1,j}^N(u_{1(i+1,j)}^{N+1} - u_{1(i+1,j)}^N) - n_{i,j}^N(u_{1(i,j)}^{N+1} - u_{1(i,j)}^N)}{dx},$$

$$G_1 = \frac{\rho_{i+1,j}^N(u_{1(i+1,j)}^{N+1} - u_{1(i+1,j)}^N) - \rho_{i,j}^N(u_{1(i,j)}^{N+1} - u_{1(i,j)}^N)}{dx}.$$

If $\frac{\partial u_1}{\partial t} > 0$ we have:

$$C_1 = \frac{n_{i,j}^N(u_{1(i,j)}^{N+1} - u_{1(i,j)}^N) - n_{i-1,j}^N(u_{1(i-1,j)}^{N+1} - u_{1(i-1,j)}^N)}{dx},$$

$$G_1 = \frac{\rho_{i,j}^N(u_{1(i,j)}^{N+1} - u_{1(i,j)}^N) - \rho_{i-1,j}^N(u_{1(i-1,j)}^{N+1} - u_{1(i-1,j)}^N)}{dx}.$$

Flow: y direction

If $\frac{\partial u_2}{\partial t} < 0$ we have:

$$C_2 = \frac{n_{i,j+1}^N(u_{2(i,j+1)}^{N+1} - u_{2(i,j+1)}^N) - n_{i,j}^N(u_{2(i,j)}^{N+1} - u_{2(i,j)}^N)}{dy},$$

$$G_2 = \frac{\rho_{i,j+1}^N(u_{2(i,j+1)}^{N+1} - u_{2(i,j+1)}^N) - \rho_{i,j}^N(u_{2(i,j)}^{N+1} - u_{2(i,j)}^N)}{dy}.$$

If $\frac{\partial u_2}{\partial t} > 0$ we have:

$$C_2 = \frac{n_{i,j}^N(u_{2(i,j)}^{N+1} - u_{2(i,j)}^N) - n_{i,j-1}^N(u_{2(i,j-1)}^{N+1} - u_{2(i,j-1)}^N)}{dy},$$

$$G_2 = \frac{\rho_{i,j}^N(u_{2(i,j)}^{N+1} - u_{2(i,j)}^N) - \rho_{i,j-1}^N(u_{2(i,j-1)}^{N+1} - u_{2(i,j-1)}^N)}{dy}.$$

Again plugging in the above equations in **Error! Reference source not found.** and discretizing the remaining terms, we get:

$$n_{i,j}^{N+1} = n_{i,j}^N - C_1 \frac{dt \left(\chi_{i,j}^N n_{i,j}^N (\rho_{i+1,j}^N - \rho_{i,j}^N) - \chi_{i-1,j}^N n_{i-1,j}^N (\rho_{i,j}^N - \rho_{i-1,j}^N) \right)}{dx^2} + \frac{dt \left(D_{i,j}^N (n_{i+1,j}^N - n_{i,j}^N) - D_{i-1,j}^N (n_{i,j}^N - n_{i-1,j}^N) \right)}{dx^2} -$$

$$C_2 \frac{dt \left(\chi_{i,j}^N n_{i,j}^N (\rho_{i,j+1}^N - \rho_{i,j}^N) - \chi_{i,j-1}^N n_{i,j-1}^N (\rho_{i,j}^N - \rho_{i,j-1}^N) \right)}{dy^2} +$$

$$\frac{dt \left(D_{i,j}^N (n_{i,j+1}^N - n_{i,j}^N) - D_{i,j-1}^N (n_{i,j}^N - n_{i,j-1}^N) \right)}{dy^2} + dt P_{i,j}^N \rho_{i,j}^{N+1} = \rho_{i,j}^N - G_1 - G_2 + dt B_{i,j}^N \quad (11)$$

$$\left(\frac{\mu}{dt} + E \right) \left(\frac{u_{1i+1,j}^{N+1} - 2u_{1i,j}^{N+1} + u_{1i-1,j}^{N+1}}{dx^2} + \frac{u_{1i,j+1}^{N+1} - 2u_{1i,j}^{N+1} + u_{1i,j-1}^{N+1}}{dy^2} \right) + F_{1i,j}^{N+1} = -\frac{\mu}{dt} \left(\frac{u_{1i+1,j}^N - 2u_{1i,j}^N + u_{1i-1,j}^N}{dx^2} + \right.$$

$$\left. \frac{u_{1i,j+1}^N - 2u_{1i,j}^N + u_{1i,j-1}^N}{dy^2} \right) + \frac{\tau_{i+1,j}^N - \tau_{i,j}^N}{dx} \quad (12)$$

$$- \left(\frac{\mu}{dt} + E \right) \left(\frac{u_{2i+1,j}^{N+1} - 2u_{2i,j}^{N+1} + u_{2i-1,j}^{N+1}}{dx^2} + \frac{u_{2i,j+1}^{N+1} - 2u_{2i,j}^{N+1} + u_{2i,j-1}^{N+1}}{dy^2} \right) + F_{2i,j}^{N+1} = -\frac{\mu}{dt} \left(\frac{u_{2i+1,j}^N - 2u_{2i,j}^N + u_{2i-1,j}^N}{dx^2} + \right.$$

$$\left. \frac{u_{2i,j+1}^N - 2u_{2i,j}^N + u_{2i,j-1}^N}{dy^2} \right) + \frac{\tau_{i,j+1}^N - \tau_{i,j}^N}{dy} \quad (13)$$

The above equations result in an algebraic system of equations, which can be written in a compact matrix form. In the following, we give an example of what equation **Error! Reference source not found.** will look like in the compact matrix form:

$$\begin{aligned} \left(\frac{\mu}{dt} + E\right) A_1 u_1^{N+1} &= \frac{\mu}{dt} A_2 u_1^N + \tau_1^N, \\ \left(\frac{\mu}{dt} + E\right) A_1 u_2^{N+1} &= \frac{\mu}{dt} A_2 u_2^N + \tau_2^N, \end{aligned} \quad (14)$$

with the matrix A_1 given by the following evolution matrix form:

$$\begin{bmatrix} \frac{2}{dx} + \frac{2}{dy} & \frac{-1}{dx} & 0 & \frac{-1}{dy} & 0 & \dots & \dots & \dots & \dots & 0 \\ \frac{-1}{dx} & \frac{2}{dx} + \frac{2}{dy} & \frac{-1}{dx} & 0 & \frac{-1}{dy} & \ddots & \vdots & \vdots & \vdots & \vdots \\ 0 & \frac{-1}{dx} & \ddots & 0 & 0 & 0 & \ddots & \vdots & \vdots & \vdots \\ \frac{-1}{dy} & 0 & 0 & \ddots & \frac{-1}{dx} & \ddots & \frac{-1}{dy} & \ddots & \vdots & \vdots \\ 0 & \frac{-1}{dy} & \ddots & \frac{-1}{dx} & \ddots & \frac{-1}{dx} & \ddots & \frac{-1}{dy} & \ddots & \vdots \\ \vdots & \ddots & 0 & \ddots & \frac{-1}{dx} & \ddots & 0 & \ddots & \ddots & 0 \\ \vdots & \vdots & \ddots & \frac{-1}{dy} & \ddots & 0 & \ddots & \ddots & \ddots & \frac{-1}{dy} \\ \vdots & \vdots & \vdots & \ddots & \frac{-1}{dy} & \ddots & \ddots & \ddots & \ddots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \ddots & \ddots & \ddots & \ddots & \frac{-1}{dx} \\ 0 & \dots & \dots & \dots & \dots & \dots & 0 & 0 & \frac{-1}{dx} & \frac{2}{dx} + \frac{2}{dy} \end{bmatrix}.$$

We simulated wound healing using systems derived for both one-dimensional and two-dimensional cases using the scientific programming language Scilab with the following parameters from the literature. In the one-dimensional case, we considered a line domain to represent damaged skin, whereas, in the two-dimensional, we considered a rectangular domain to represent damaged skin.

- $R = 0.2$
- $s = 1$,
- $\rho_i = 0.1$,
- $\mu = 1$,
- $\varepsilon = 0.01$,
- $E = 0.01$,
- $\tau = 0.1$.

Comment [Han jz6]: $R = 0.2$ $S = 1$ in this paper represents the meaning?

4 Results

The following sections present and discuss the finding from solving the coupled system numerically. We will show the results in two parts: a two-dimensional case and a three-dimensional case.

4.1 Two-dimensional case

The results from the simulation reveal that cell density recovers quickly following an injury to the skin (**Figure 1a**). It can also be seen that cell density recovers fully, while the extracellular matrix takes a long time to recover and in most cases, it never recovers fully (**Figure 1b**). These results are consistent with what Murray and Oster [8] found from their model. The cells move rapidly into the wound, and gradually the movement of cells slows down (**Figure 2**) when the wound has fully developed into scar tissue. Again, these results are consistent with what was previously found in the case of two-dimensional.

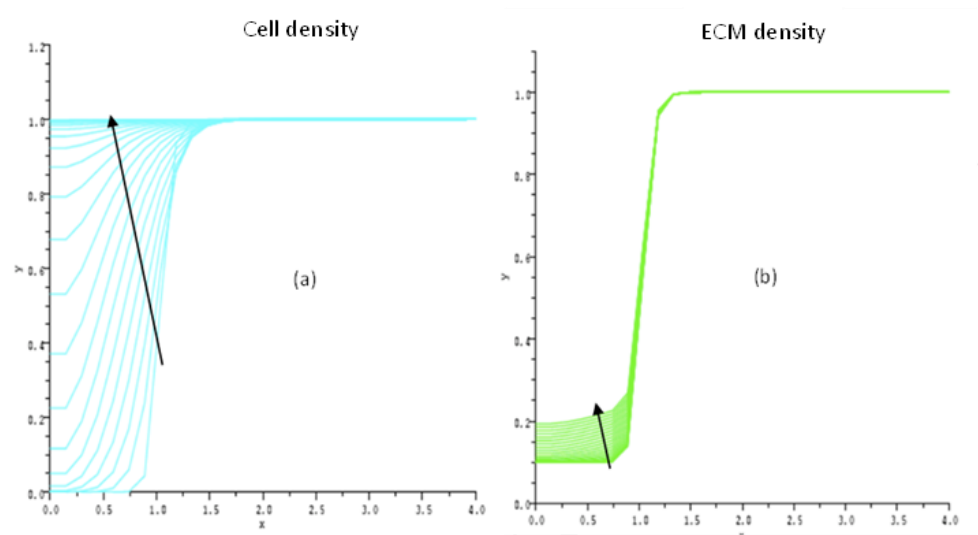


Figure 1. Evolution of cell density (a) within the damaged wound and evolution of extracellular matrix (ECM) density (b) within during the wound healing. The arrow indicates how cell density or ECM density evolves with time during wound healing.

Comment [Han jz7]: The content pointed by the arrow in the figure is not prominent.

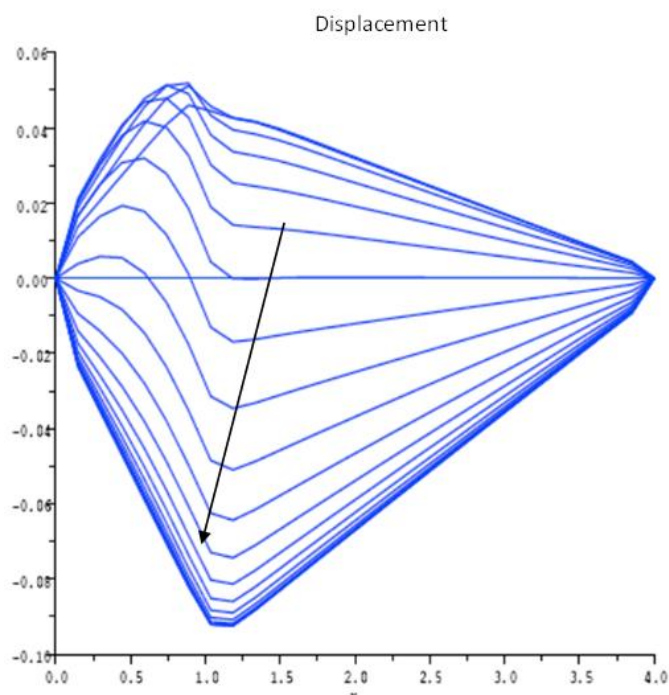


Figure 2. displacements of cells to rapidly replace the dead cells during the wound healing. The arrow shows the direction of movement of cells with time during wound healing.

4.2 Three-dimensional case

The same pattern observed in two dimensional is again observed in the three-dimensional: cell density recovers quickly (**Figure 3**), but the ECM density still takes a long time to heal completely (**Figure 4**). The red arrows show that the cell density and ECM density evolve with time during wound healing. The movement of cells is dependent on the direction of flow; some cells move in the x -direction (**Figure 5a**) and others in the y -direction (**Figure 5b**) to replace the in cells. Again we observed that after the recovery of the injured, the movement of cells slowed down in both directions.

Comment [Han jz8]: The phenomenon in the diagram needs explanation and analysis.

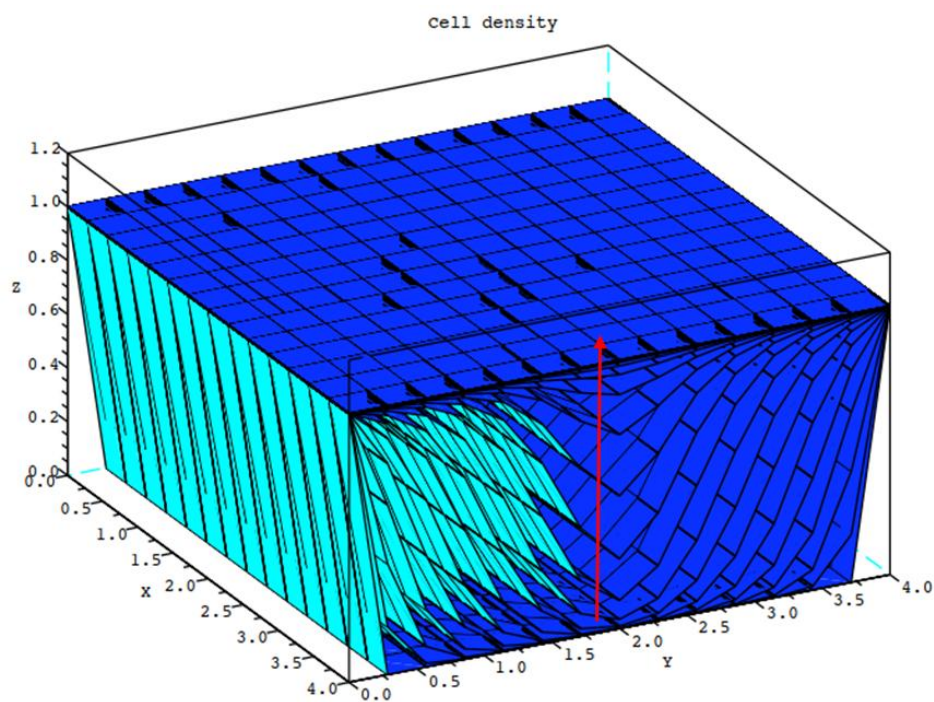


Figure 3. Cell density evolution within the wound. *The red arrow indicates how the cell populated the wound with time during the healing process.*

Comment [Han jz9]: The meaning of the arrow is explained in the text.

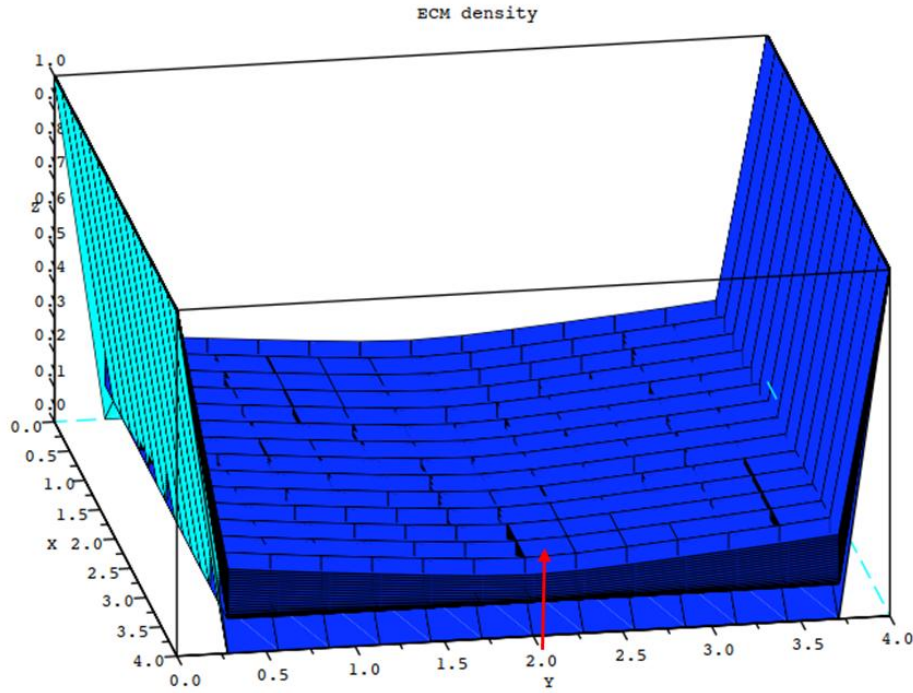


Figure 4. ECM recovery during wound healing following the injured tissue. The red arrow indicates how slow the ECM is recovering with time.

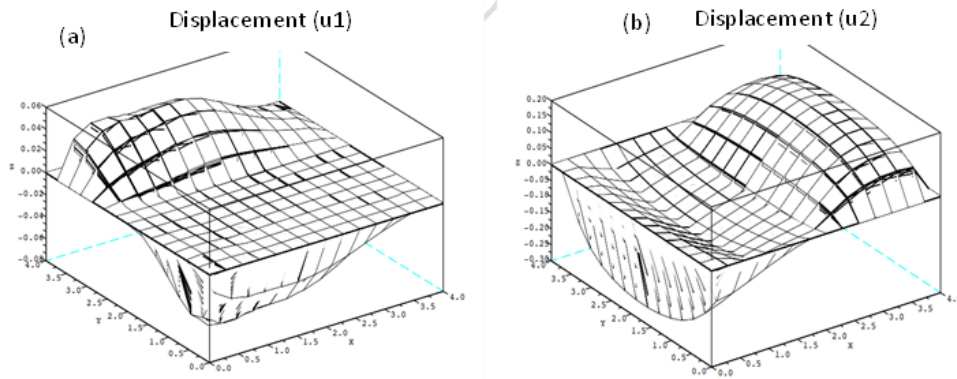


Figure 5. The displacements of cells within the injured tissue during the healing process.

5 Discussions and conclusions

In this paper, we used the coupled reaction-diffusion, transport and viscoelastic system of Partial differential equations to model wound healing in both two-dimensional and three-dimensional cases. We applied the implicit finite difference scheme with the Euler forward scheme for the time variable to discretize this coupled system of equations. During the discretization, attention was given to the flow direction during the cell migration within and around the wound domain. We took advantage of the stability of the implicit scheme.

Comment [Han jz10]: Conclusion needs refining.

However, we ran into computational costs due to evolving sparse matrices and their inverses which had to be computed at each iteration.

The results from this simulation have shown that cell density returns to its normal functioning within a short time following the injury to the tissue. In contrast, the extracellular matrix takes a long time to return to its normal functioning state. The displacements of the cells have also shown that cells migrate fast from the normal tissue to the injured tissue. When the wound has returned to its close to a normal functioning state, the movement of cells has been shown to slow down.

This study can be extended to be applied to epithelial tissue injuries because it has been suggested that more than 90% of malignant tumours in adult mammals occur in epithelial tissues. It is then of the highest importance to understand the dynamic regulations of focal adhesions involved during the cell migration in epithelial lines. This mathematical model can also be utilized to describe the closure behaviour from a pure kinematic point of view of a particular cell sheet, the Madin-Darby canine kidney (MDCK) monolayer cell sheet. But to do this, a global optimization algorithm needs to be performed to make parameter identification based on biological experiments. This computational tool developed will assist in shedding some original light on the mechanics which occur inside the cells sheet.

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